A NOVEL PROCESS FOR THE PREPARATION OF SITAGLIPTIN

The present invention is directed to a process for the preparation of enantiomerically enriched β-amino acid derivatives which are important chiral building blocks and intermediates in pharmaceuticals. More specifically, the invention pertains to a novel process for practically convenient and economically producing enantiomerically enriched β-amino acid derivatives which are useful for the synthesis of amide inhibitors of dipeptidyl peptidase IV like Sitagliptin, which have been used to treat type 2 diabetes.
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FIELD OF INVENTION

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BACKGROUND OF INVENTION

Sitagliptin is 3(R)-amino-l(3-(trifluoromethyl)-5,6,7,8-tetrahydro-(1,2,4)triazolo(4,3-a)pyrazin-7-yl)-4-(2,4,5-trifluorophenyl)butan-l-one of Formula I and its pharmaceutically acceptable salts has the following chemical structure

![Chemical Structure of Sitagliptin](attachment:image.png)

Formula I

Sitagliptin phosphate is a glucagons-like peptide 1 metabolism modulator, hypoglycemic agent and dipeptidyl peptidase IV inhibitor. Sitagliptin phosphate is currently marketed in the United States under the trade name JANUVIA™ in its monohydrate form. JANUVIA™ is indicated to improve glycemic control in patients with type 2 diabetes mellitus. Sitagliptin phosphate is described in PCT publication No WO 2005/003135.
Sitagliptin can be obtained by the condensation of the two key intermediates. The first intermediate is (3R)-amino-4-(2,4,5-trifluorophenyl)butanoic acid (Synthon 1) having the following formula

![Formula Ila]

The second intermediate is 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (Synthon 2) having the following formula

PCT publication No WO 2003/004498 discloses a method of introducing a chiral amine group using a chiral pyrazine derivative and to prepare sitagliptin by Arndt-Eistert Homologation using t-butyloxycarbonylamino-4-(2,4,5-trifluorophenyl)-butyric acid.
wherein,
Boc is t- butoxycarbonyl,
TEA is trimethyl amine,
HOBt is 1-hydroxybenzotriazole,
EDC is N-ethyl-N’-(3-dimethylaminopropyl)carbodiimide,
DIPEA is N,N-diisopropylethylamine.

PCT publication NO WO 2004/087650 refers to the synthesis of sitagliptin via the stereoselective reduction of methyl 4-(2,4,5-trifluorophenyl)-3-oxobutanoate to produce the sitagliptin intermediate (S^methyl 4-(2,4,5-trifluorophenyl)-3-hydroxybutanoate. The said stereoselective reduction is performed by hydrogenation with H₂ and (S)BINAP-RuCl₂ catalyst in presence of hydrochloric acid followed by inversion of stereochemical centre, achieved by Mitsunobu cyclization of (3S)-N-benzyloxy-3-hydroxy-4-(2,4,5-trifluorophenyl)butyramide. The process is illustrated in the below scheme:
wherein,

BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
EDC is N-ethyl-N,N,N-trimethylaminopropyl)carbodiimide,
Bn is benzyl,
DIAD is diisopropyl azodicarboxylate,
NMM is N-methylmorpholine,
ACN is acetonitrile.

In PCT publication No WO 2004/085661, the reduction is performed on a substituted enamine (S)-2-(Z)-4-(3-trifluoromethyl)5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl-l-(2,4,5-trifluorophenyl)-4-oxobut-2-en-2ylamino)-2-phenylacetamide with PtO₂.

PCT publication No WO 2005/097733 discloses the preparation of sitagliptin by enantioselective hydrogenation of (2Z)-4-oxo-4-[3(trifluoromethyl),5,6-dihydr[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)but-2-en-2amine in the presence of rhodium metal precursor complexed with a chiral mono or biphosphine ligand.
wherein,

DMAP is 4-(dimethylamino)pyridine,
DMAc is N,N-Dimethylacetamide.

WO 2006/081151 describes the asymmetric hydrogenation which is carried out in presence of ammonium salt and a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand.

Unfortunately, these processes based on carrying out an asymmetric hydrogenation suffer from operation difficulty due to the high hydrogen pressure of about 100-500 psi needed to carry out the reaction. That means that special facilities which tolerate the work at high pressure are required. Another drawback of the asymmetric hydrogenation is the very high cost of the catalyst and its ligand. Although Josiphos ligands are commercial, their cost is still very high.

WO 2009/084024 discloses process for the preparation of Sitagliptin and its pharmaceutically acceptable salts by resolving the amine with a resolving agent. Most of the time the said patent application describe the resolving agent is dibenzyl-L-tartaric acid. The said patent describes that the chiral purity obtained is only 85-90% that too after repeated recrystallizations.
wherein,

\[ X = \text{Chiral acid} \]

WO 2009/085990 discloses process for the preparation of Sitagliptin by using phenylalkyl amine as a chiral handle for crystallization of diastereomeric mixture as shown below:
WHEREIN,

\[ X = \text{Reagent}, \]
\[ Y = \text{Acid residue} \]

WO 2009/064476 discloses a process for intermediate compounds in the synthesis of Sitagliptin, 3-amino-4-(2,4,5-trifluorophenyl)but-2-enoic acid alkyl ester and the stereoselective reduction of these compound to give (3R)-amino-4-(2,4,5-trifluorophenyl)butanoic acid of the following formula:
The WO 2009/064476 discloses a process for preparing the above intermediate from corresponding imine ester of following formula:

![Chemical Structure](image)

with chiral catalyst and hydrogen. This PCT also describes reduction of imine ester with reducing agent in presence of chiral acids. The chiral organic acid employed is (R or S)-mandelic acid.

PCT publication No WO 2010/131025 discloses a process for the preparation of enantiomerically enriched β-amino acid derivatives such as β-amino esters useful for the synthesis of enantiomerically enriched biologically active molecules such as sitagliptin. The process utilizes the resolution of the racemate with mandelic acid which is shown below:
US 2011/0130587 A1 discloses a process for preparing single enantiomers of β-amino phenylbutyric acid derivatives and pharmaceutically acceptable salts thereof, which affords the desired compounds having special optical configuration. The process comprises a step of chemical synthesis and a step of resolving the optical isomers of β-amino phenylbutyric acid derivatives with a resolving agent.

The obtained R-β-amino phenylbutyric acid derivatives (II) have high optical purity, and the total yield of the accumulative resolution of the leavo and the dextro isomer is up to above 70%.
The chiral pharmaceutical intermediates, R-β-amino-phenylbutyric acid derivatives of formula (I) are prepared as outlined in the following scheme:

wherein,
Ar = 2,4,5-trifluorophenyl.
Ia: \( R^1 = H, R^2 = H \),
Ib: \( R^1 = \text{ethyl}, R^2 = H \),
Ic: \( R^1 = H, R^2 = \text{tert}-\text{butoxyl carbonyl} \).

Resolving agents used in the above reaction are dibenzoyl-D-tartaric acid, dibenzoyl-L-tartaric acid, di-p-toluoyl-D-tartaric acid, di-p-toluoyl-L-tartaric acid.

PCT publication No 2010/122578 also discloses a process for the preparation of Sitagliptin and intermediates which is shown below:
US 2011/0213149 A1 discloses the synthesis of β-amino acid derivatives of formula (I) and its salts by a novel process. The process comprises the reduction of a protected or unprotected prochiral β-amino acrylic acid or derivative thereof, by using borane containing reducing agents at atmospheric pressure. The resulting racemic β-amino compound is resolved to a pure stereoisomer of formula (I), specifically to (2R)-4-
oxo-4-[3-CTrifluoromethyl)-5,6-dihydrol[1,2,4]triazolo[4,3-alpyrazin-7(8H)-yl]-l-(2,4,4-trifluorophenyl)butan-2-amine.


The enantioselective hydrogenation of enamine III was performed and the resultant amine was protected with N-tert-butylcarbamate followed by a crystallization method for enhancing the enantiomeric purity by employing camphorsulphonic salt. The process can be shown as follows:
Wherein,

\[ R = H \text{ or Me} \]

As discussed above, the prior-art teaches a variety of asymmetric synthesis to prepare enantiomerically enriched β-amino acids and their derivatives in the preparation of Sitagliptin. The prior-art also illustrates the importance of β-amino acid derivatives as key intermediates for the synthesis of sitagliptin. However, the prior-art suffers from various disadvantages with respect to commercial production. These above mentioned asymmetric synthesis provide products with low purity. Hence, a further purification is needed to control the stereo-selectivity and improve optical purity.

Therefore, there is a great need for simple, convenient, inexpensive and commercially viable process for the synthesis of sitagliptin and its intermediates with a commercially acceptable yield and purity.

Optical resolution is a particularly convenient technique for the commercial production of chiral molecules as the technique eliminates the economic problems associated with asymmetric synthesis. Surprisingly, the resolution of racemic β-amino acids or derivatives to obtain enantiomerically enriched β-amino acids or
derivatives and their subsequent conversion into enantiomerically enriched sitagliptin free base and its dihydrogen phosphate salt is not widely reported in the prior-art.

The present inventors have developed a method of resolution of racemic β-amino acid derivatives, in particular β-amino esters, to obtain enantiomerically pure sitagliptin and salts thereof.

**OBJECTIVE OF THE INVENTION**

The main object of the present invention is to provide a novel process for the preparation of compound of Formula I and its pharmaceutically acceptable salts.

Another main objective of the invention is to provide an improved process for effectively resolving a mixture of (R) and (S) isomers β-amino acid in any proportion, to obtain either of the isomer in an enantiomeric purity of at least 99%.

Another object of the present invention is to prepare an enantiomerically enriched β-amino acid derivative of Formula II and its salts.

Another object of the present invention is further conversion of Formula II to Sitagliptin.

In another embodiment of the invention, there is provided a resolution method of racemic β-amino acid derivative of Formula II by using suitable chiral resolving agents.

In another embodiment of the present invention is to provide a racemization process for enrichment of unwanted isomer of Formula II and also Formula I.
Another embodiment of the present invention is the resolution of Formula I as per scheme I.

**SUMMARY OF THE INVENTION**

The present invention relates to a novel process for the preparation of β-amino acid intermediates of Formula Ila and its enantiomers lib.

Wherein R is C1-5 alkyl.

Comprising the steps of:

i) Resolving the racemic β-amino acid derivatives of Formula II

Wherein R is defined as above

With a compound of Formula Ila or IIlb

Where in Ar denotes phenyl and substituted phenyl and
$R_1 = \overset{O}{\bigcirc} C - R_2$ and $R_2$ is aryl, alkyl, O-alkyl, O-phenyl, O-arylalkyl
to give compound of optically enriched isomer of Formula Ila or IIb.

These compounds of Formula IIa and its enantiomer IIb are independently converted
to Formula I or its enantiomers.

Besides the instant invention also relates to a novel process for resolution of racemic
sitagliptin of Formula IV as shown in the following scheme.
wherein $A_r$ denotes phenyl and substituted phenyl and

\[ R_1 = \text{aryl, alkyl, O-alkyl, O-phenyl, O-arylalkyl} \]

to give Sitagliptin of Formula I.

The compounds of Formula IVa and Formula IVb are independently converted to Formula I or its enantiomers.
DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises a process for the preparation of sitagliptin free base and its salts with chiral acids by a simple, reliable, convenient and commercially acceptable process as detailed below.

The present invention provides a simple, convenient process for the preparation of compound of Formula Ila or lib.

The present invention also provides a process for the preparation of enantiomerically enriched sitagliptin free base and sitagliptin dihydrogen phosphate using enantiomerically enriched β-amino acid derivative of Formula Ila or lib.

A preferred embodiment of the present invention involves a process of resolving racemic compound of Formula II with compound of Formula Ila or IIlb to obtain enantiomerically enriched β-amino acid derivative of Formula Ila or lib.

Preferably the enantiomerically enriched β-amino acid derivative obtained is converted into enantiomerically enriched sitagliptin of Formula I or its dihydrogen phosphate salt.

In a preferred embodiment of the present invention, the process comprises the steps of:

a) treating the racemic β-amino acid derivative of Formula II with a compound of Formula Ila or IIlb to obtain enantiomerically enriched β-amino acid salts and
b) optionally crystalizing the enantiomerically enriched β-amino acid salt and
c) dissolving or suspending the enantiomerically enriched β-amino acid salt obtained in step (a) or (b) in an organic solvent or water or a mixture thereof and adjusting
the pH of the solution or suspension with a base to obtain an enantiomerically enriched β-amino acid derivative of Formula IIa or Formula lib
d) conversion of Formula IIa or Formula lib to sitagliptin base and its pharmaceutically acceptable salts.

The compounds of Formula IIia or IIib include but not limited to are N-acetyl-L-phenylalanine, (S)-l-2-pentamido-3-phenylpropanoic acid, (S)-l-(phenoxy carbonyl) pyrrolodine-2-carboxylic acid.

A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl)butanoate was dissolved in acetone and heated to reflux temperature. Subsequently, N-acetyl-D-phenylalanine dissolved in acetone was added to the reaction mixture and again heated to reflux for about 1 hour. Then the reaction mixture is allowed to come to ambient temperature and the obtained resulting precipitate was collected by filtration, washed with acetone. The obtained precipitate was then treated with a base in a biphasic mixture to obtain (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl)butanoate having a chiral purity of 97.94%. The obtained compound was further recrystallized to achieve greater chiral purity.

A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl)butanoate is dissolved in acetone at 50-55 °C followed by addition of (S)-2-pentanamido-3-phenylpropanoic acid in acetone. The reaction mixture is heated to reflux for 1 hr and then allowed to come to 20 °C to 25 °C. The resulting precipitate is collected by filtration, washed with acetone. The resulting solid was basified to give (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl)butanoate having a chiral purity of 91.98% by HPLC. The obtained chiral compound was further recrystallized to achieve greater chiral purity.

The obtained compounds were characterized by spectroscopic methods.
The resolution step can be performed in alcoholic solvents, chlorosolvents, ketone solvents, hydrocarbon solvents, nitrile solvents, ester solvents, ether solvents, polar solvents, polar aprotic solvents and mixtures thereof.

The obtained \((R)\) 3 amino-4-(2,4,5-trifluorophenyl)butanoate was further converted into Sitagliptin and its pharmaceutically acceptable salts thereof by known methods in the art.

The chiral N-acetyl-D-Phenylalanine was recovered by acidifying the aqueous layer by cone. HCl and then filtered and dried under vacuum.

The present invention also includes stereo-selective process for the preparation of sitagliptin for which process comprises the following.

a) treating the racemic compound of Formula IV with an enantiomerically pure compound of Formula IIa or IIib.

b) isolating the salt formed from sitagliptin and chiral acid of formula IIa or IIib.

c) converting the salt from step (b) to sitagliptin phosphate of Formula I.

The racemic Sitagliptin and N-acetyl-D-phenylalanine in methanol was refluxed for about 30 minutes and allowed to cool to ambient temperature. The reaction mixture was maintained at ambient temperature for about 15 hrs. The resulting precipitate was collected by filtration, washed with methanol and dried to obtain Sitagliptin having a chiral purity of >99 \(\%\) by HPLC.

The obtained sitagliptin was subsequently converted to pharmaceutically acceptable salts.
The resolution step of resolving racemic Sitagliptin can be performed in alcoholic solvents, chlorosolvents, ketone solvents, hydrocarbon solvents, nitrile solvents, ester solvents, ether solvents, polar solvents, polar aprotic solvents and mixtures thereof.

The optical purity of the optically active intermediate compounds was determined by chiral HPLC methods.

The present invention has certain advantages over the prior-art methods like the use of n-acetyl-l-phenylalanine of Formula III, it is possible to resolve the enantiomers of Formula II with high yield. On the other hand, prior-art processes are either with respect to the resolution agent for the separation of isomers or use entirely different agents for the optical resolution. There are no suggestions in the prior-art which might point the skilled person towards the use of compound of Formula III as the resolution agent.

The resolving agents employed in the present invention are recoverable in a quality fit for recycling as a resolving agent, thereby making the process economical.

The Sitagliptin prepared by the process of the present invention are suitable for pharmaceutical composition.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without being departing from the spirit and scope thereof.

Certain aspects of the invention are further illustrated by the following examples which are not construed as limiting the scope of the invention.
EXAMPLE

Example 1
Preparation of (R) Ethyl 3-amino-4-(2, 4, 5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (5 gm, 0.019 moles) was dissolved in acetone (50 ml) and heated to 50 to 55°C, charged N-acetyl-D-phenylalanine (3.3 gm, 0.015 moles) by dissolving in acetone (50 ml). The reaction mixture was heated to reflux for 1 hr then allowed to come to 20 to 25°C. The resulting precipitate was collected by filtration washed with acetone (10 ml) and then re-crystallized from acetone (100 ml). After twice re-crystallization, 3.0 gm of a white solid was obtained.

2.5 gm of white solid was then treated with a base in a biphasic mixture to obtain 1.6 gm of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate having a chiral purity of 97.94% by HPLC. Chiral acid N-acetyl-Z)-phenylalanine was recovered by acidifying the aqueous layer by cone HC1, filtering the solid and dried under vacuum.

Example 2
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (20 gm, 0.076 moles) was dissolved in acetone (200 ml) at 50 to 55°C and charged N-acetyl-Z)-phenylalanine (12.64 gm, 0.06 moles) by dissolving in acetone (200 ml). The reaction mixture was heated to reflux for 1 hr then allowed to come to 20 to 25°C. The resulting precipitate was collected by filtration, washed with acetone (10 ml) and then re-crystallized from acetone (330 ml) to give 8.5 gm of desired compound, which was subsequently treated with a base in a biphasic mixture to obtain 6.5 gm of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate having a chiral purity of HPLC 94.75% .
Example 3
Preparation of (S) Ethyl 3-amino-4-(2, 4, 5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (5 gm, 0.019 moles) was dissolved in methanol (20 ml) at 20 to 25°C, N-acetyl-L-phenylalanine solution (2 gm, 0.009 moles in 10 ml methanol) was added. The reaction mixture was allowed to stir for 1 hr at 20 to 25°C, the resulting precipitate was collected by filtration, washed with methanol (10 ml), re-crystallized in acetone (50 ml). After re-crystallization 2.0 gm of a white solid was treated with a base in a biphasic mixture to obtain 0.75 gm of (S) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate having a chiral purity of 96.06% by HPLC.

Example 4
Preparation of (R) Ethyl 3-amino-4-(2, 4, 5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (1.3 gm, 0.0049 moles) was dissolved in acetone (25 ml) at 50 to 55°C followed by addition of (S)-l-(phenoxy carbonyl) pyrrolodine-2-carboxylic acid (0.65 gm, 0.002 moles in 25 ml of acetone). The reaction mixture was heated to reflux for 1 hr and then allowed to cool to 20 to 25°C, the resulting precipitate was collected by filtration, washed with acetone (5 ml) to give 3 gm of white solid.

This was basified as mentioned in Example 1 to give (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (0.15 gm) with a chiral purity of 87.61% by HPLC.

Example 5
Preparation of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (2 gm, 0.0076 moles) was dissolved in acetone (20 ml) at 50 to 55°C followed by addition of (S)-2-pentanamido-3-phenylpropanoic acid (1 gm) in acetone (20 ml). The reaction
mixture was heated to reflux for 1 hr and then allowed to come to 20 to 25 °C, the resulting precipitate was collected by filtration, washed with acetone (5 ml). The resulting white solid was basified as in Example 1 to give (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (0.5 gm) having a chiral purity of 91.98% by HPLC.

Example 6

Preparation of (S) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate

A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (2 gm, 0.0076 moles) was dissolved in ethyl acetate (10 ml) at 50 to 55°C followed by addition of (R)-2-pentanamido-3-phenylpropanoic acid (1 gm) by dissolving in ethyl acetate (10 ml). The reaction mixture was heated to reflux for 1 hr and then allowed to come to 20 to 25°C, the resulting precipitate was collected by filtration, washed with ethyl acetate (5 ml) to give a white solid (2.1 gm) which was then treated with a base in a biphasic mixture to give (S) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (0.75gm) having a chiral purity of 80.55% by HPLC.

Example 7

Preparation of (R) Methyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate

A racemic mixture of Methyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (10 gm, 0.04 Omoles) and (S)-2-pentanamido-3-phenylpropanoic acid (5.3 gm, 0.020 moles) dissolved in ethyl acetate (200 ml) was heated to 65 to 70°C for 1 hr and then allowed to come to 20 to 25°C. The reaction mass was allowed to stir for 15 hrs at 20 to 25°C and the resulting precipitate was collected by filtration, washed with ethyl acetate (20 ml). Re-crystallization of wet mass was carried out in ethyl acetate (100 ml).

Dry wt = 4.2 gm.

Melting point -120.7-124.9° C, SOR in 1% in Methanol +20.658 °.
The obtained product was treated with aq. sodium bicarbonate and extracted with Dichloromethane to give 3.0 g m o f (R) Methyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate having a chiral purity of 100% by HPLC.

Example 8
Preparation of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (20 gm, 0.076 moles) and (S)-2-pentanamido-3-phenylpropanoic acid (12.04 gm, 0.045 moles) dissolved in ethyl acetate (400 ml), heated to 65 to70°C and refluxed for 1 hr and then allowed to cool to 20 to 25°C, the reaction mass was allowed to stir for 15 hrs at 20 to 25°C, the resulting precipitate was collected by filtration, washed with ethyl acetate (20 ml). The product was re-crystallized in ethyl acetate (100 ml).

Dry wt.=10.5 gm.
Melting point-140.7-141.8°C, SOR in 1% in Methanol +22.46°
Chiral HPLC-99.63%

Example 9
Preparation of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (5 gm, 0.019 moles) and (S)-2-pentanamido-3-phenylpropanoic acid (5.02 gm, 0.019 moles) dissolved in ethyl acetate (100 ml), the reaction mass was heated to 65 to70°C and refluxed for 1 hr and then allowed to cool to 20 to 25°C. The reaction mass was stirred for 15 hrs at 20 to 25°C. The resulting precipitate was collected by filtration, washed with ethyl acetate (20 ml), and re-crystallized from ethyl acetate (100 ml).

Dry wt.=3.2 gm.
Melting point-139.4-139.8°C, SOR in 1% in Methanol +20.03°
Chiral HPLC-98.76%
Example 10
Preparation of (R) Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate
A racemic mixture of Ethyl 3-amino-4-(2,4,5-trifluorophenyl) butanoate (5 gm, 0.019 moles) and (S)-2-pentanamido-3-phenylpropanoic acid (4.015 gm, 0.0152 moles) dissolved in ethyl acetate (100 ml) and the reaction mass as heated to 65 to 70°C. The reaction mass was refluxed for 1 hr, allowed to come to 20 to 25°C. The reaction mass was allowed to stir for 15 hrs at 20 to 25°C and the resulting precipitate was collected by filtration, washed with ethyl acetate (20 ml). The title compound was re-crystallized from ethyl acetate (100 ml) to give 2.5 gm of product. Melting point 139.8-142.1°C, SOR in 1% in Methanol +22.700°
Chiral HPLC-98.30%

Example 11
Preparation of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid
(R)-Methyl-4-(2,4,5-trifluorophenyl)butanoate (3g, 0.012 moles) in THF (12.5 ml) was added to aq. NaOH (1g in 12.5 ml H₂O) at room temperature and cooled to 0-5°C. To this Boc anhydride (3.16 gm, 0.014 moles) was added slowly and maintained at this temperature for 4-5 hrs. After completion of reaction at 0-5°C additional lot of aq. NaOH (1gm in 12.5 ml) and THF (12.5 ml) were added to the reaction mass and allowed to stir at 20-25°C for 5 hrs for completion of ester hydrolysis. The reaction mass was acidified with 30% aq.citric acid at pH 5.5-6.0. The resulting solution was extracted with MDC (3x100 ml). The organic layer was washed with brine, dried over sodium sulphate and concentrated to give a thick residue. This thick mass was triturated with n-Hexane to give 1.8 gm of product.
SOR (1% CHCl₃) + 26.928°, Melting point 123.9-127.2°C
R isomer content by chiral HPLC 99.40%
Example 12
Preparation of (R)-tert-butyl-4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-
[l,2,4]triazolo-[4,3-a]pyrazin-7-(8H-yl)-1-(2,4,5-trifluorophenyl)butane-2yI-
carbamate
A mixture of Boc acid (1.8 gm, 0.005 moles) from Example 11 and
carbomyldiimidazole (1.05 gm, 0.0064 moles) in ethylacetate (20ml) was reacted
with 3-(trifluoromethyl)-5,6,7,8-tetrahydro[l,2,4]triazolo[4,3-a]pyrazine-
hydrochloride (Synthon 2) (1.48 gm, 0.0064 moles) at room temperature. The
resulting reaction mass was heated to 50-55°C for 15 hrs. After completion of
reaction by TLC the reaction mass was quenched with water (18ml) at room
temperature and cooled to 10-15°C. The precipitated product was collected to give
2.2 gm of product.
SOR (1% in methanol) +3.6° Melting point 189-192.8°C
Chiral purity by HPLC 99.30%

Example 13
Preparation of Sitagliptin
(R)-tertbutyl-4-oxo-4-(3-trifluoromethyl)-5,6-dihydro-[l,2,4]-triazolo-[4,3-a]pyrazin-
7-(8H-yl)-1-(2,4,5-trifluorophenyl)butane-2-7'-carbamate (1.92 gm, 0.0039 moles) in
IPA (20 ml) was treated with conc.HCl (5.7 ml) at room temperature. Reaction mass
was heated to 50-55 °C and maintained for 5 hrs. After completion of reaction, the
reaction mass was basified and the product was extracted with ethylacetate (2>20ml),
dried and concentrated to give Sitagliptin (1.5 gm).
Chiral Purity 99.7%
Example 14
Preparation of Sitagliptin Phosphate
Sitagliptin base (1 gm) in IPA (30ml) was treated with water (0.5ml) and H₃PO₄ (0.39gm) was added at 20-25°C. The reaction mass was heated to 60-65°C and maintained at same temperature for 3-4 hrs. The precipitated product was cooled, filtered and washed with IPA (20ml) and dried.
Dry Wt.- 0.725 gm, HPLC >99%
Chiral HPLC-99%, SOR-1% in water -24°

Example 15
Preparation of Sitagliptin by resolution
Racemic Sitagliptin (3 gm, 0.0073moles) and N-acetyl-D-phenylalanine (1.53gm, 0.0073moles) in methanol (120 ml) were refluxed for 30 minutes, allowed to cool to 20 to 25°C and maintained at same temperature for 15hrs. The resulting precipitate was collected by filtration, washed with methanol (10 ml) and dried at 50 to 55°C under vacuum.
Dry Wt.-0.5gm
Chiral HPLC (R) isomer- >99%

Example 16
Preparation of (S) -2-pentanamido-3-phenylpropanoic acid
Charge Z-phenylalanine (100 gm) in 4 N of NaOH solution at 20 to 25°C (pH should in between 11-12). Reaction mass was cooled to 0 to 5°C and valeryl chloride (75 gm) was added at same temperature drop wise with maintaining reaction mass pH in between 11-12 by addition of 4N NaOH. After addition, reaction mass allowed to sir for 1hr at 20 to 25°C. Then 400 ml of ethyl acetate was charged and pH was adjusted between 1-2 with cone. HCl at 20 to 25°C. Reaction mass stirred for 15 minutes at the same temperature and separated the layers and aqueous layer extracted with
2x200ml of ethyl acetate. Combined organic layer washed with 200ml of water
followed by 200ml of brine. Organic layer treated with Na₂S₀₄ and distilled out
under vacuum below 45-50°C to get 105 gm of off white product.
Melting range-94.4-10.2°C
SOR 1% in Methanol +19.3 16°

Example 17
Preparation of N-Acetyl-D-phenylalanine
To a stirred solution D-phenylalanine (20gms) in water (120 ml) at 0 to 5°C, aq.
sodium hydroxide solution was added maintain its pH 11-12. To this basic amino acid
solution, acetic anhydride (37 ml) and aq. sodium hydroxide were simultaneously
added at a temperature between 10-15°C. After completion of addition, reaction mass
was kept under stirring for 30 minutes at 20 to 25°C, then the reaction mixture was
acidified to pH 1 with concentrated HCl. The resulting ppt was filtered, re-
crystallized from water to afford N-acetyl-D-phenylalanine as white solid.
Melting point at about 163.9-165.3°C
SOR at about -39.2° (1% in methanol)

Example 18
Preparation of N-Acetyl-L-phenylalanine
To a stirred solution L-phenylalanine (20gms) in water (120 ml) at 0 to 5°C, aq.
sodium hydroxide solution was added maintain its pH 11-12. To this basic amino acid
solution, acetic anhydride (37 ml) and aq. sodium hydroxide were simultaneously
added at a temperature between 10 to 15°C. After completion of addition, reaction
mass was kept under stirring for 30 minutes at 20 to 25°C, then the reaction mixture
was acidified to pH 1 with concentrated HCl. The resulting ppt was filtered, re-
crystallized from water to afford N-acetyl-D-phenylalanine as white solid.
Melting point at about 163.9-165.3°C
SOR at about +39.2° (1% in Methanol)
CLAIMS

1. A process for the preparation of β-amino acid intermediate of Formula Ila and its enantiomers lib

   \[
   \begin{align*}
   &\text{Formula Ila} \\
   &\text{Formula lib}
   \end{align*}
   \]

   wherein R denotes C<sub>1-5</sub> alkyl.

   comprising the steps of

   i) resolving the racemic β-amino acid derivatives of Formula II

   \[
   \text{Formula II}
   \]

   wherein R is defined as above

   with a compound of Formula IIia or IIlib

   \[
   \begin{align*}
   &\text{Formula IIia} \\
   &\text{Formula IIlib}
   \end{align*}
   \]

   wherein Ar denotes phenyl and substituted phenyl and

   \[
   R_1 = \text{O} \quad \text{and} \quad R_2 \text{ is aryl, alkyl, O-alkyl, O-phenyl, O-arylalkyl}
   \]

   to give compound of optically enriched isomer of Formula Ila or lib.
2. A process according to claim 1 step(i), characterized in that the resolution is carried out with (S)-2-pentanamido-3-phenylpropanoic acid or (R)-2-pentanamido-3-phenylpropanoic acid.

3. A process according to claim 1 step(i), characterized in that the resolution is carried out N-acetyl-L-phenylalanine or N-acetyl-D-phenyl alanine.

4. The process according to claim 1 step(i), is carried out in a suitable solvent.

5. The process of claim 1 step(i), wherein the solvent is selected from alcoholic solvents, chlorosolvents, ketone solvents, hydrocarbon solvents, nitrile solvents, ester solvents, ether solvents, polar solvents, polar aprotic solvents and mixtures thereof.

6. The process of claim 1 step(i), wherein the obtained compound of Formula Ila or Formula lib is further converted to Sitagliptin or its isomers comprising the steps of
   i) protection of Formula Ila or lib by a suitable protecting group followed by hydrolysis of ester group
   ii) condensing the N-protected acid compound of Formula Ice

   ![Formula IIC]
wherein p denotes N-Protecting group

with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazole[4,3-a]pyrazine

iii) removing the protecting group to obtain Sitagliptin which is optionally converted to pharmaceutically acceptable salts.

7. The process according to claim 6, step(i) wherein the protecting group employed are BOC, CBz, acetyl etc.

8. A Novel process for the preparation of resolution of racemic sitagliptin of Formula IV as shown in the following scheme.
wherein Ar denotes phenyl and substituted phenyl and

\[ R_1 = \text{c-R}_a \text{d R}_2 \]

to give Sitagliptin of Formula I and its enantiomers.

9. A process according to claim 8, characterized in that the resolution is carried out with N-acetyl-L-phenylalanine or N-acetyl-D-phenyl alanine
10. A process according to claim 8, characterized in that the resolution is carried out
with (S)-2-pentanamido-3-phenylpropanoic acid or (R)-2-pentanamido-3-
phenylpropanoic acid.

11. The process according to claim 8, where in the reaction is carried out in a
suitable solvent.

12. The process of claim 11, wherein the solvent is selected from alcoholic solvents,
chlorosolvents, ketone solvents, hydrocarbon solvents, nitrile solvents, ester
solvents, ether solvents, polar solvents, polar aprotic solvents and mixtures
thereof.

13. The process according to claim 12, wherein the solvent employed is methanol.

14. A pharmaceutical composition comprising R-sitagliptin or a pharmaceutically
acceptable salts thereof, obtained by a process according to claim 1 and 8.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D 487/-; C07C 227/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI;EPDOC;CNKI;JEE;CNPAT;STN (registry, caplus); sitagliptin, resolution, enantiomer, racemic, optical,pentamido, phenylpropanoci, acetyl, alanaine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>CN 101959406 A (MERCK SHARP&amp;DOHME CORP.) 26 Jan. 2011 (26.01.2011) see claim 1</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  ‘A’ document defining the general state of the art which is not considered to be of particular relevance
  ‘E’ earlier application or patent but published on or after the international filing date
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“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
06 Jun. 2013 (06.06.2013)

Name and mailing address of the ISA/CN
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6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088
Facsimile No. 86-10-62019451

Authorized officer
WANQ Bo
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**A. CLASSIFICATION OF SUBJECT MATTER**

C07D 487/04 (2006.01) i
C07C 227/16 (2006.01) i